Rheumatoid Arthritis: Early Diagnosis, Early Treatment

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Disclosures

- None

At the end of this talk, you should be able to:

- Recognize the clinical features and differential diagnosis of early rheumatoid arthritis (RA)
- List some key factors in the pathogenesis of RA
- Describe the laboratory evaluation helpful in early diagnosis
- Have an understanding of treatment strategies in RA
- Know what you can do to help the rheumatologist in the co-management of RA

Case

- 37 year-old woman
- 7-week history of progressive polyarthralgias
- Pain in wrists, hands and feet
- Swelling in some joints, decreased hand function
- Morning stiffness for 3 hours
- Excessive fatigue
- ROS otherwise non-contributory
- Some relief from ibuprofen

Case

- Exam with swelling and tenderness at the bilateral wrists, 2nd MCPs, and 2nd PIPs, and bilateral MTP joints; no nodules
- Rest of exam including skin is normal
- Labs with mild normocytic anemia, mildly elevated ESR 28, normal renal and liver function tests
- Radiographs of hands with some soft tissue swelling around the wrists and PIPs, otherwise normal

Case

- Does she have inflammatory arthritis?
  - Yes
  - History of joint swelling, early morning stiffness lasting ≥30 minutes, systemic symptoms such as fatigue, improvement of symptoms with anti-inflammatory medication
  - Objective evidence of joint swelling and tenderness on examination
  - Raised ESR or CRP, normocytic normochromic anemia; could also have thrombocytosis, low albumin, raised alkaline phosphatase
- Could she have rheumatoid arthritis?
  - Yes

Rheumatoid Arthritis- Definition

- Chronic (>6 weeks), systemic, inflammatory arthritis
- Typically symmetrical joint involvement with polyarticular pattern
- Small joints of the hands and feet (wrists, MCPs, PIPs, MTPs)
- RF or CCP antibody may be positive (70-80%)
- Associated with erosive joint disease and extra-articular features

Reality can be more complex!

- Objective signs may be lacking or have been suppressed by anti-inflammatory medication
- Joint swelling can be difficult to identify in obese patients
- The sensation that joints are swollen may be reported even by some patients with fibromyalgia
- Osteoarthritis as well as RA can cause morning stiffness, though in osteoarthritis it usually lasts less than 30 minutes
- Inflammatory markers such as the ESR or C-reactive protein (CRP) are normal in about 60% of patients with early RA
- In a patient with preceding osteoarthritis, radiographic changes can be misleading, especially if those suggestive of inflammatory arthritis have not yet developed.

Furthermore… Variable RA presentations

- Polymyalgic onset- elderly, presents acutely with stiffness predominantly in the shoulders and pelvic girdle. ESR high usually. Good response to prednisone 15-20 mg/d. Later peripheral joint inflammation appears.
- Palindromic onset- recurrent episodes of pain, swelling, redness affecting any one joint or several joints at a time, lasting 24-48 hours, mimicking gout or pseudogout
- Systemic onset- non focal weight loss, fatigue, depression, fever, extra-articular features such as serositis, articular manifestations absent or subtle.
- Persistent monoarthritis- one single large joint, such as knee, shoulder, ankle or wrist. May mimic chronic infection.

Other conditions may look like RA

- Postviral arthritis—e.g. parvovirus, mumps, rubella, hepatitis B and C
- Seronegative spondyloarthritis—e.g. psoriatic arthritis, inflammatory bowel disease, reactive arthritis
- Connective tissue diseases—e.g. systemic lupus erythematosus, scleroderma, MCTD, vasculitis
- Inflammatory Osteoarthritis
- Crystal arthritis—e.g. polyarticular gout, pseudogout
- Miscellaneous—e.g. sarcoidosis, thyroid disease, infective endocarditis, paraneoplastic syndromes

Additional Investigations

- Review of Systems, social and exposure history
- Laboratory tests

Case

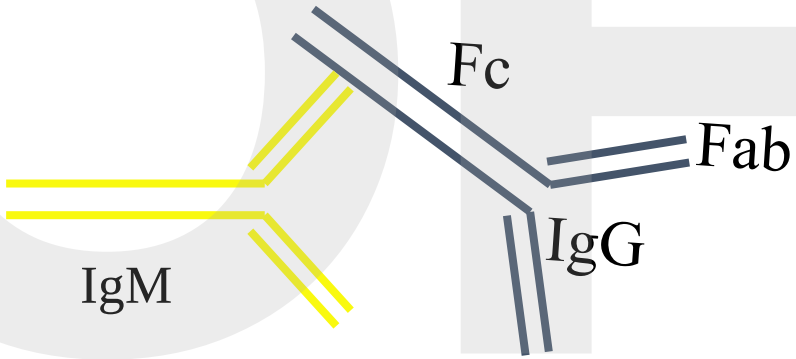
- Additional tests:
  - RF
  - CCP antibody
  - ANA
  - Urinalysis
  - Viral panel
  - Xrays

Additional Investigations

- Rheumatoid factor

Serologic Testing in RA: Rheumatoid Factor

- Rheumatoid Factor



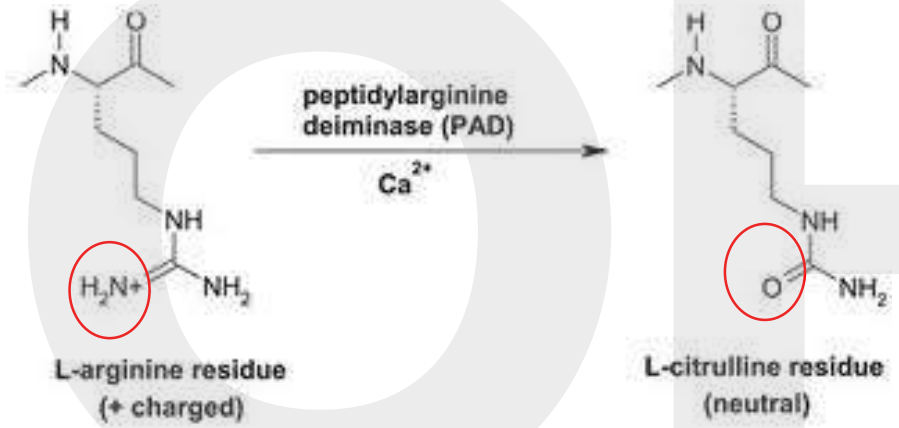
- Sensitivity 60-80%
- Specificity <70%
- Other causes of +RF
  - Infections
  - Malignancy
  - Other rheumatic diseases
  - Health

Additional Investigations

- Rheumatoid factor
- CCP antibody

Serologic Testing in RA: CCP Antibody

Anti-cyclic citrullinated peptide antibody



Citrullination:

- Post translational deamination of arginine to citrulline
-Occurs during cell-death and tissue inflammation
-Important consequences for the structure and function of proteins
-New epitopes, immunogenic

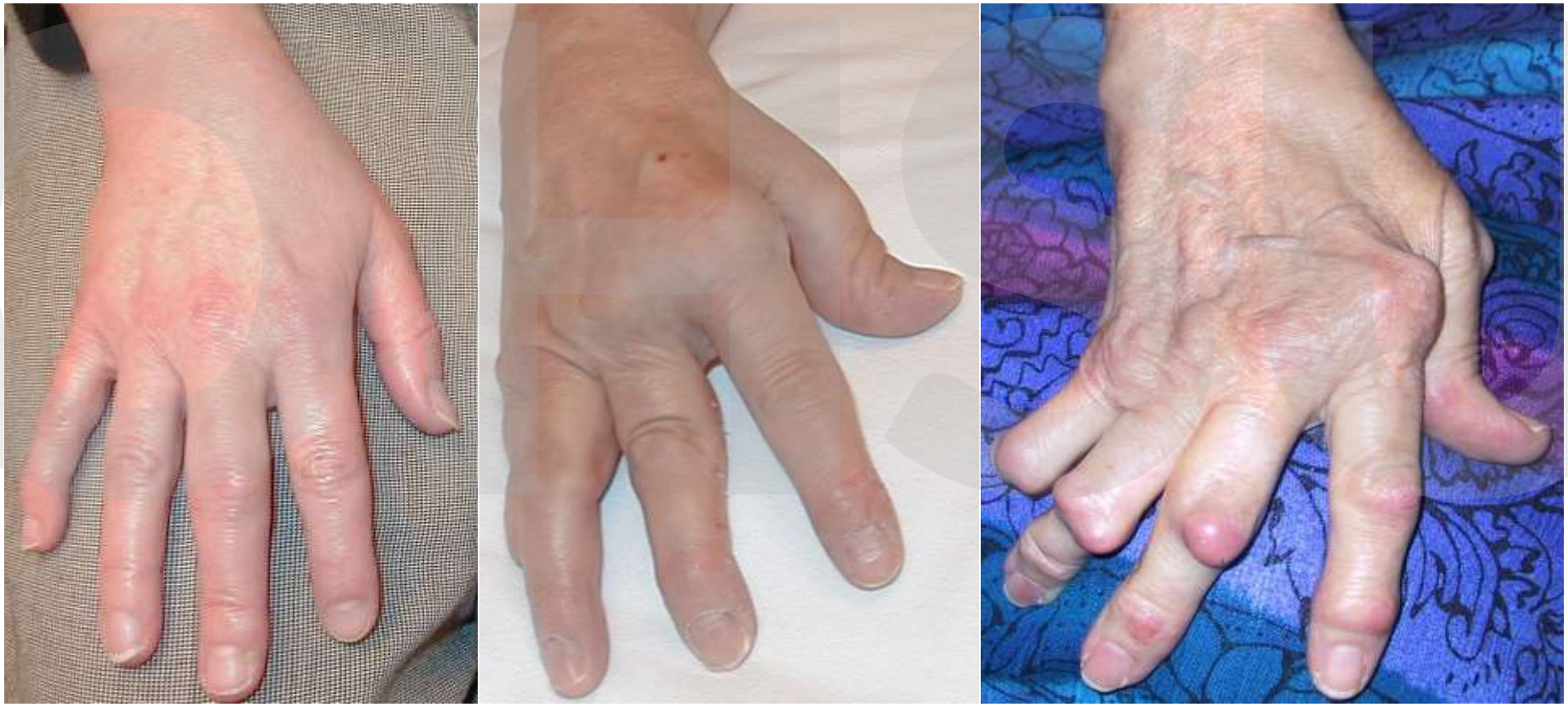
- Implicated in the pathogenesis of RA
- Sens 70% Spec 95%
- 40% of RF negative patients are ACPA+
- Detected in preclinical state
- Predicts more severe course and erosive disease

Additional Investigations

- Rheumatoid factor
- CCP antibody
- Antinuclear antibody—good screening test for SLE but sometimes positive in conditions including RA (30%) and in health
- Urinalysis—microscopic hematuria/proteinuria can indicate connective tissue disease or vasculitis
- Viral antibody titers—parvovirus IgM, hepatitis B/C, HIV
- Serum urate/synovial fluid analysis—to assess probability of gout/pseudogout
- Plain radiographs of hands and feet—can be normal in early RA or show periarticular soft tissue swelling/osteopenia/marginal erosions; erosions occur earlier in feet, so the feet should be X-rayed even in patients without foot symptoms

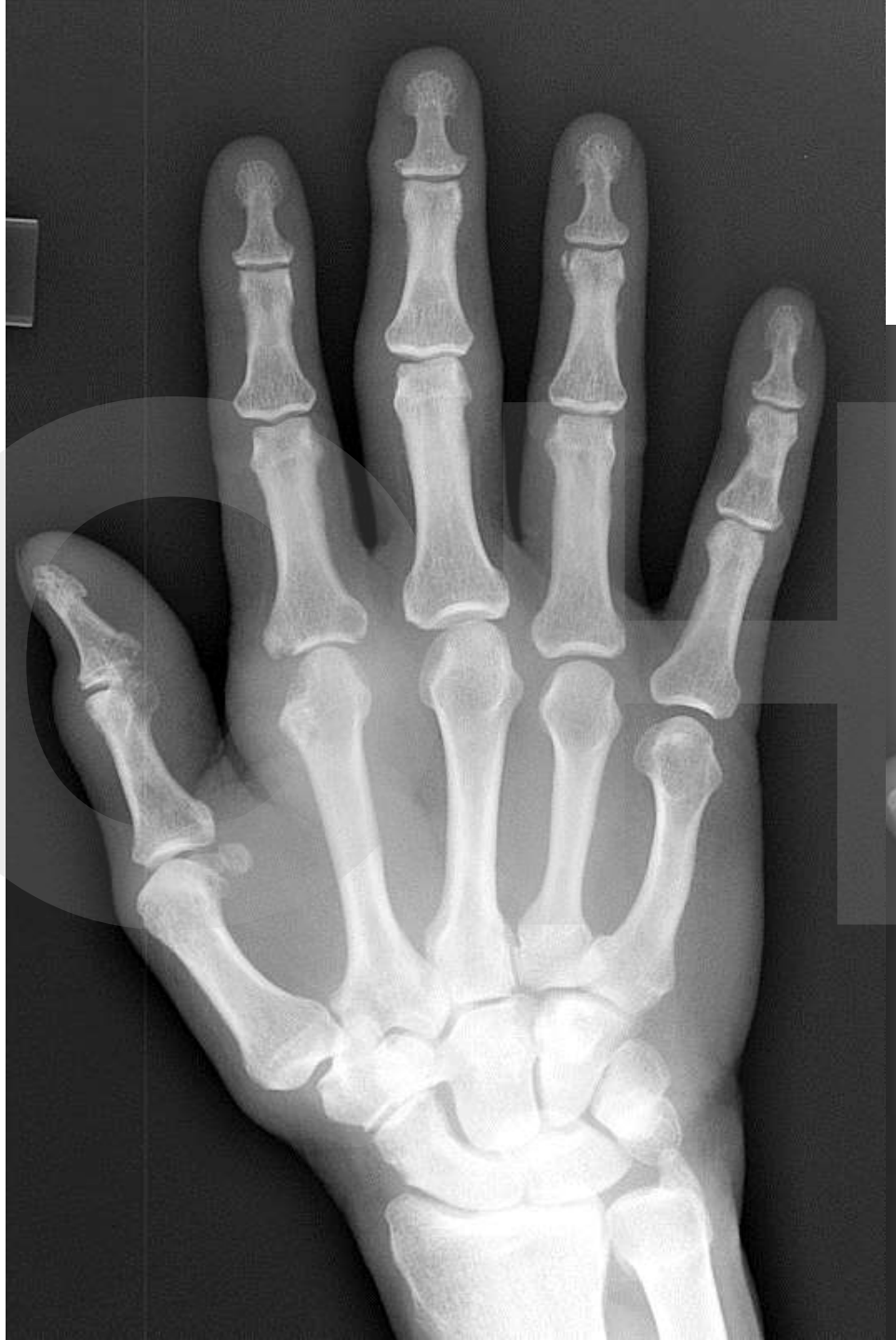
Stages of RA

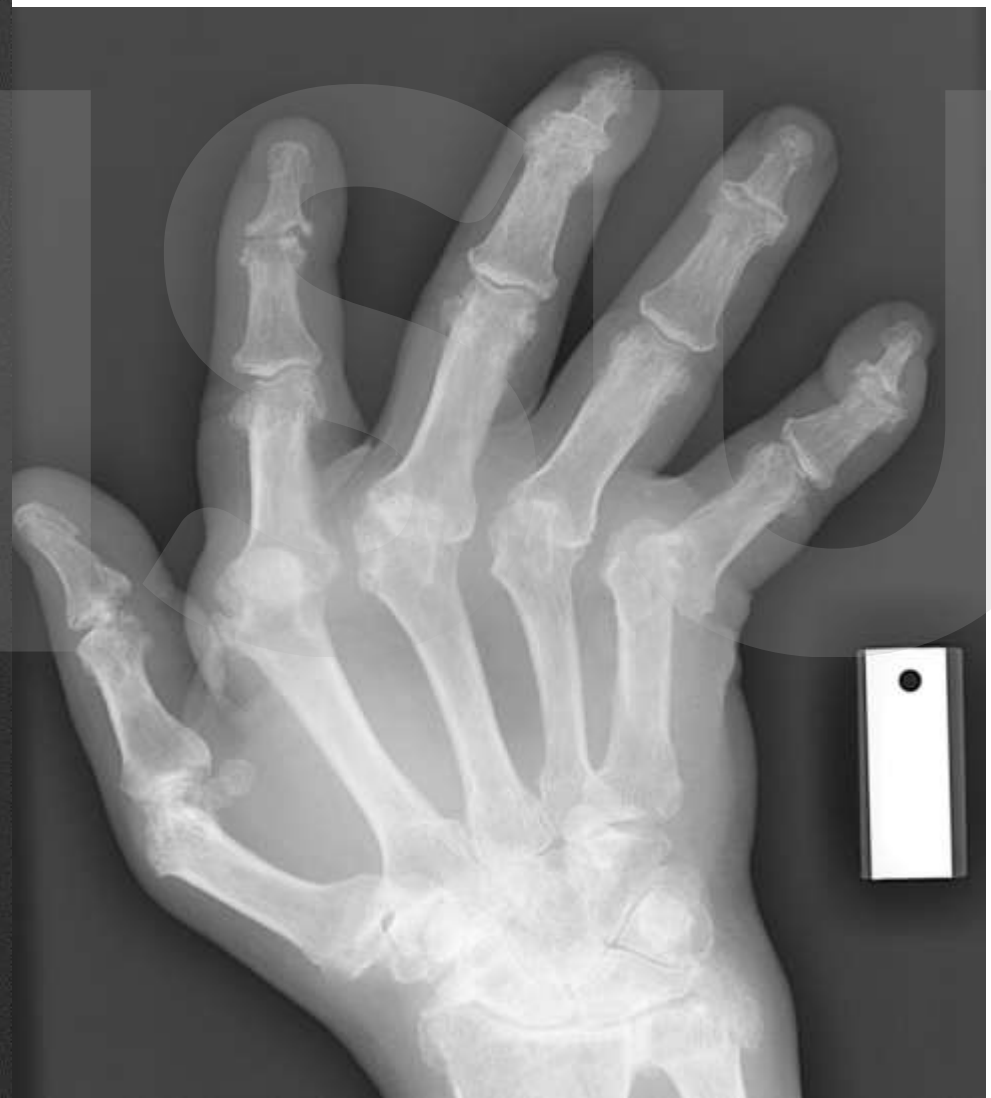
Early **Intermediate** **Late**



Courtesy of J. Cush, 2002.

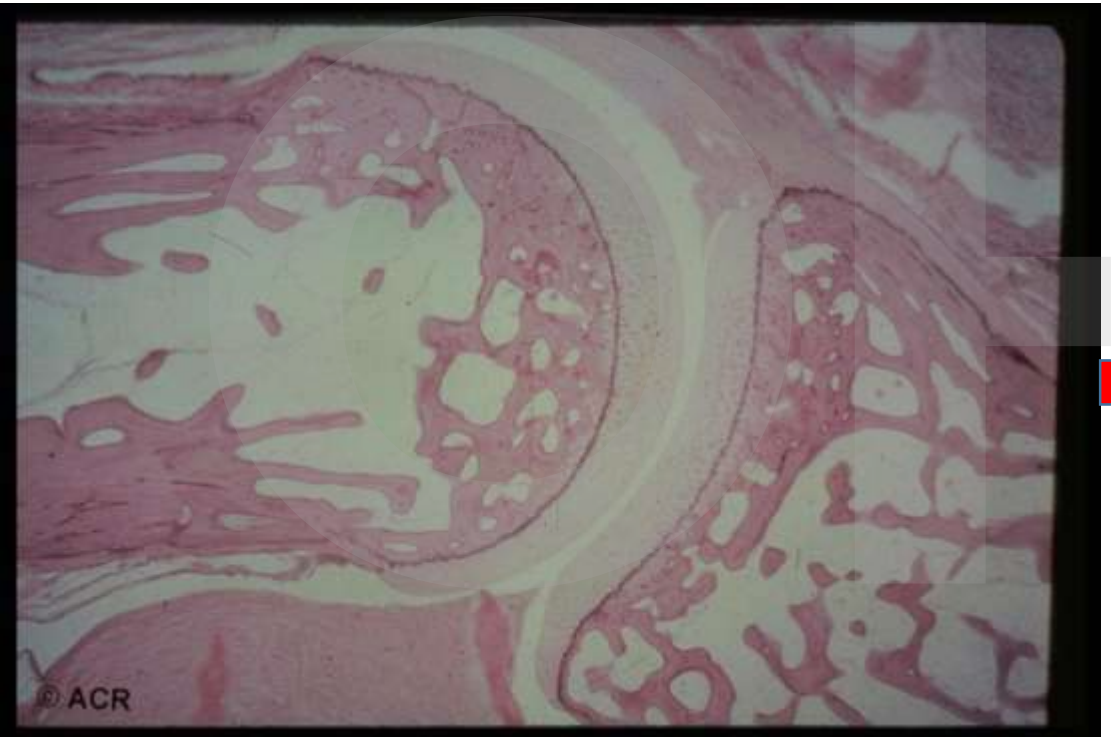
RA- Radiographs in early stages may be normal or subtle changes



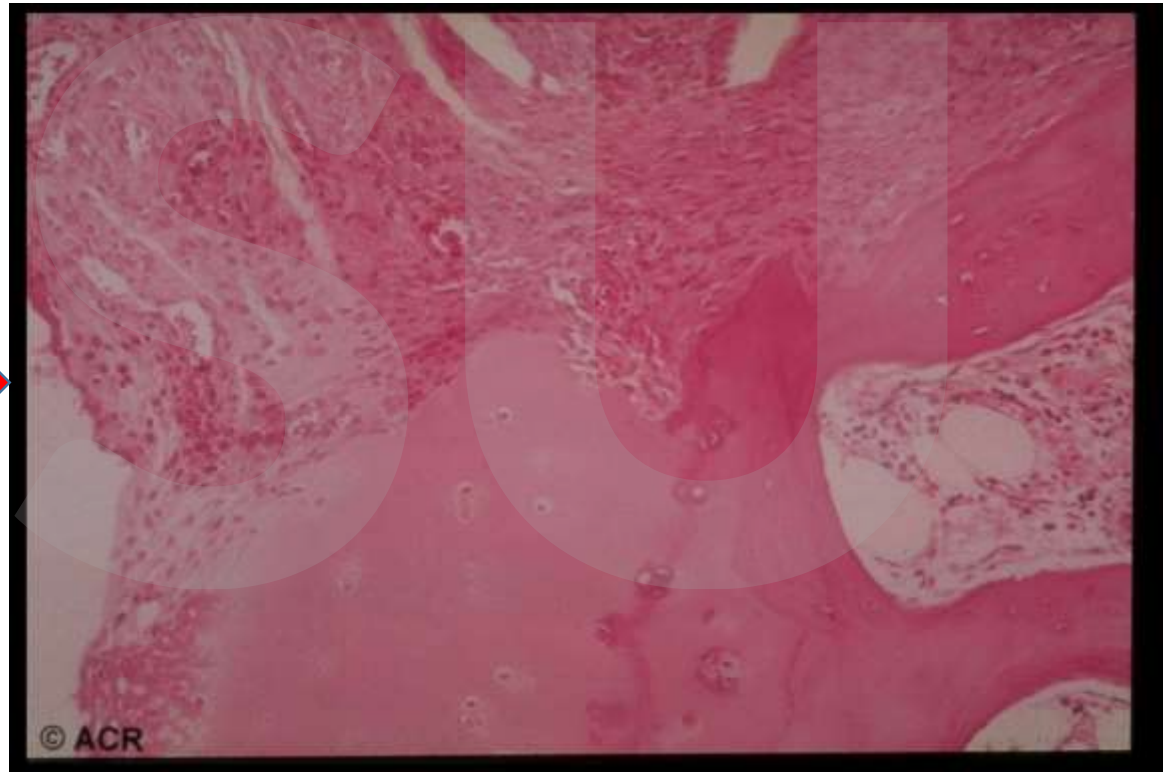


Cartilage and Subchondral Bone Invasion

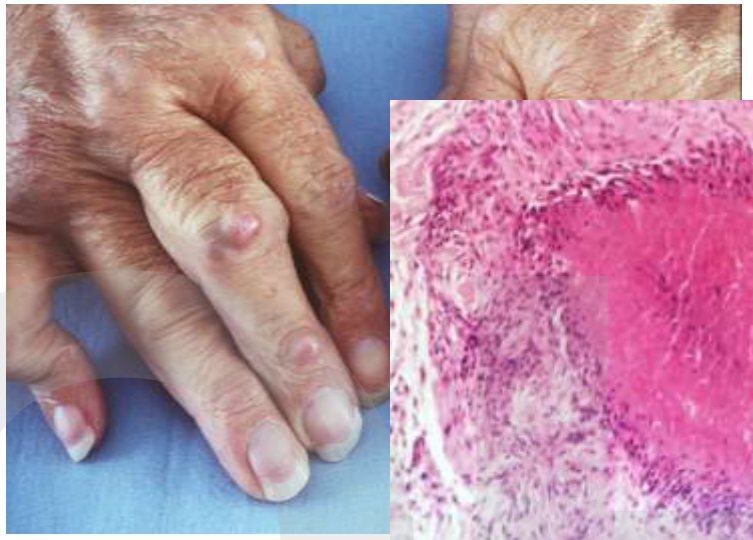
Normal

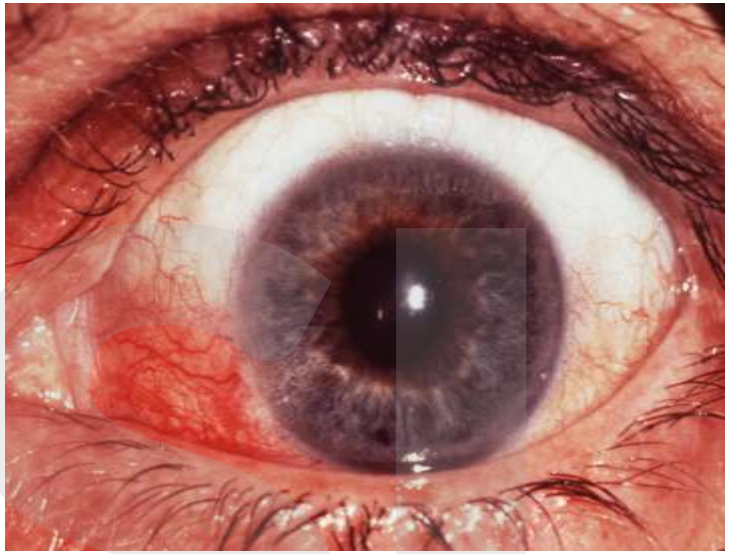


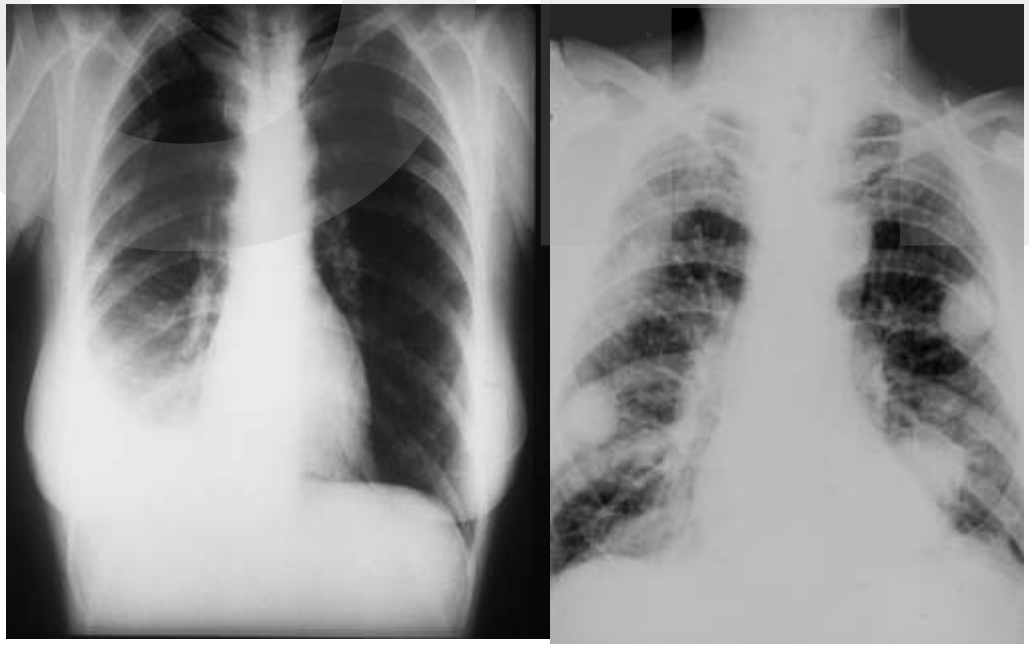
Pannus invasion

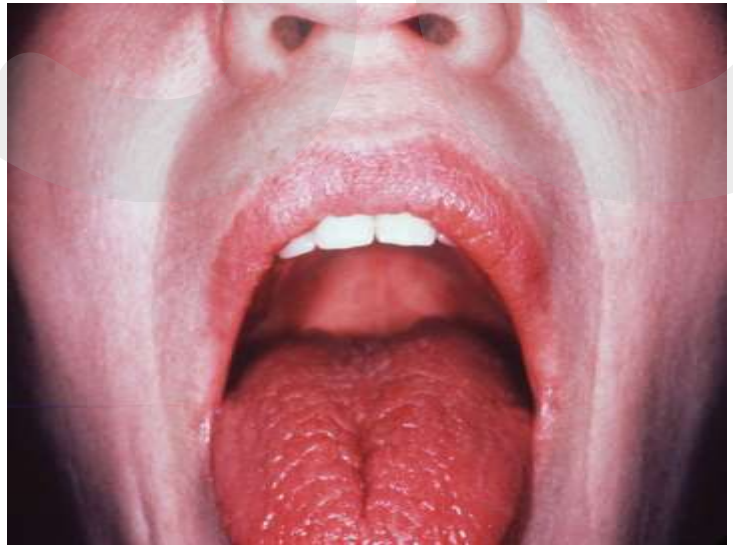


RA- Extra-articular Manifestations

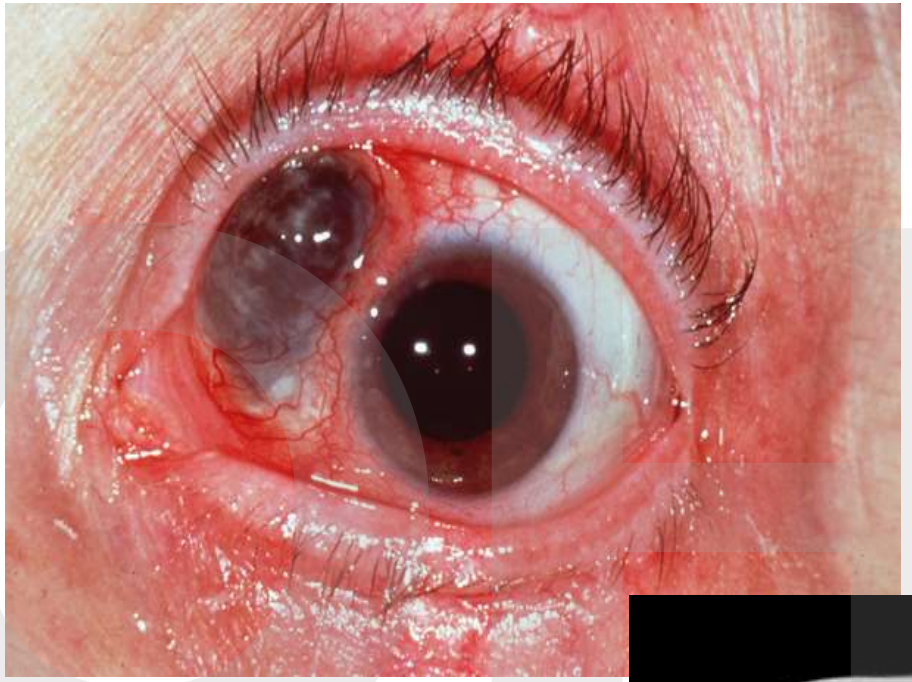


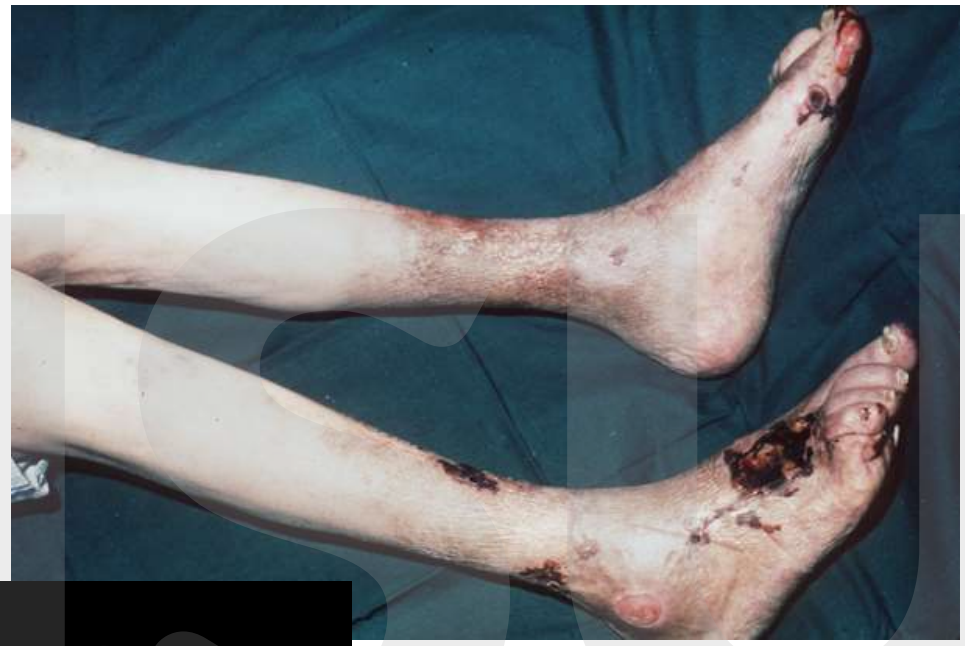


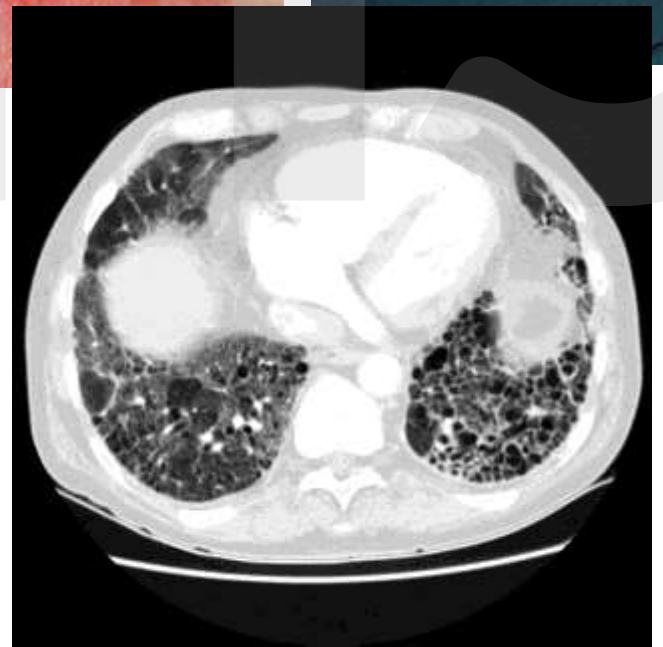




RA- Organ Threatening







ACR RA Classification- 1987

- Morning stiffness in and around the joints lasting greater than one hour
- Joint swelling of 3 or more joints
- Joint swelling of hand joints
  - wrist, MCP, PIP
- Symmetrical joint involvement
- Rheumatoid nodule
- Positive RA factor
- X-ray findings showing bony erosions

Symptoms must be ongoing for 6 weeks or longer; Need to have 4 out of 7 criteria for definitive diagnosis

ACR Classification- 2010

Table 3. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)#	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

Aletaha et al. A&R 2010

Epidemiology

- Worldwide, all ethnic groups
- Can occur at any age, but peaks between the 4th and 6th decades
- Prevalence in North America is 0.3-1.5%
- Prevalence is 2.5 times greater in women than in men
- Concordance rates among monozygotic twins 15-30%

Genes implicated in RA

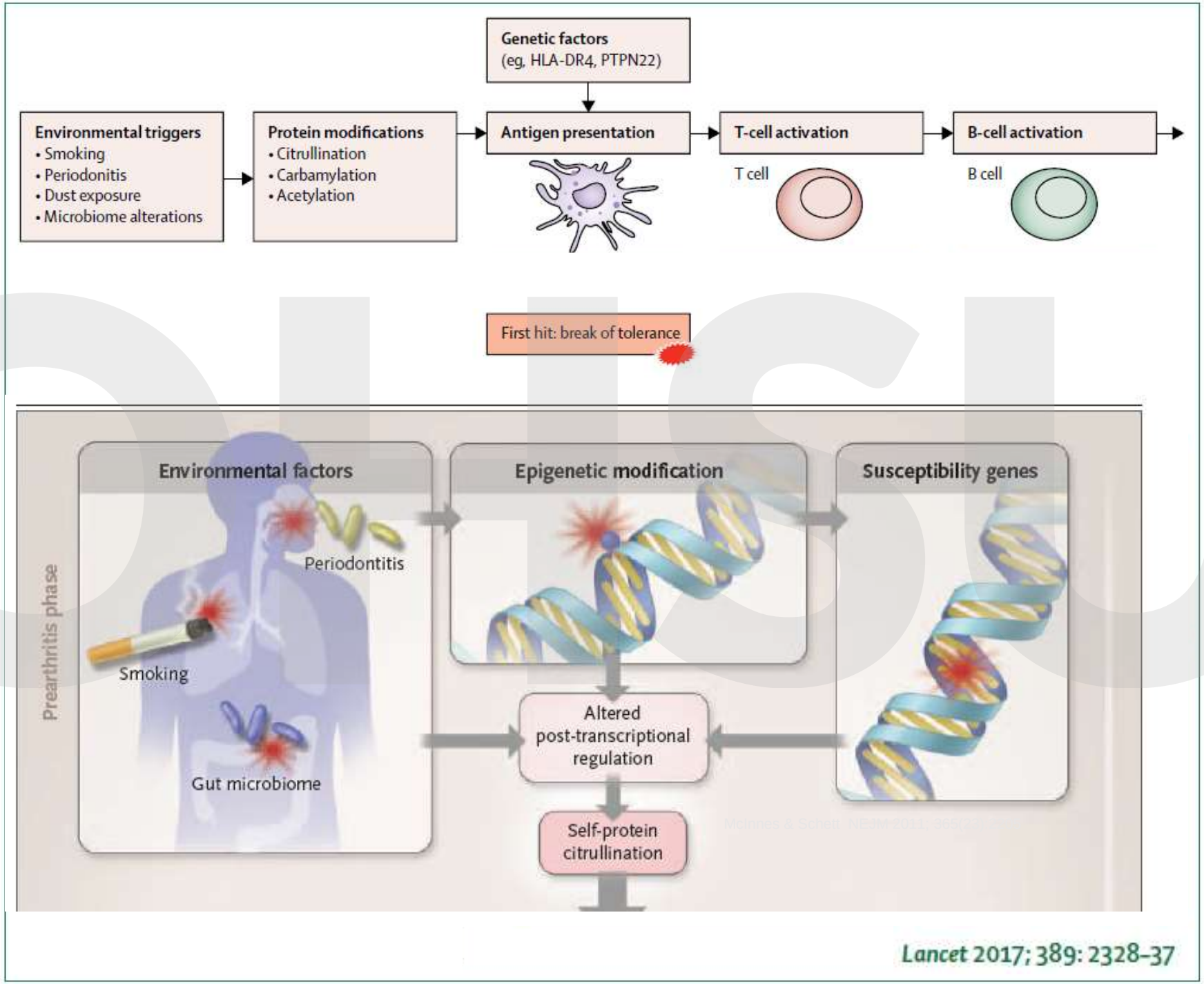
Table 1. Candidate Genes with Single-Nucleotide Polymorphisms (SNPs) Linked to Rheumatoid Arthritis and Their Potential Function in Pathogenesis.*

Candidate Gene and Pathway	SNP Locus	Function Relevant to Pathogenesis
T-cell activation		
HLA-DRB1†	6p21	HLA DRB1 allele (also known as the shared epitope) involved in MHC molecule–based antigen presentation and responsible for self-peptide selection and T-cell repertoire; first discovered and still by far the strongest genetic link to rheumatoid arthritis
PTPN22	1p13.2	Lymphocyte-specific nonreceptor tyrosine phosphatase involved in regulation of activation threshold of lymphocytes; second genetic link described in rheumatoid arthritis
AFF3	2q11.2	Transcription factor for lymphoid development
CD28	2q33.2	Costimulatory molecule for T-cell activation
CD40	20q13.12	Costimulatory molecule that enhances interactions between T and B cells and increases autoantibody production
CTLA4	2q33.2	Costimulation suppressor that regulates interactions between T cells and antigen-presenting cells
IL2RA	10p15.1	High-affinity receptor for interleukin-2 on lymphocyte subsets
IL2	4q27	Cytokine that regulates activation of T cells, particularly regulatory T cells
IL-21	4q27	Cytokine that regulates differentiation of T cells, particularly Th17, and activation of B cells
PRKCQ	10p15.1	Member of the protein kinase C family that regulates T-cell and macrophage activation
STAT4	2q32.3	Transducer of cytokine signals that regulate proliferation, survival, and differentiation of lymphocytes
TAGAP	6q25.3	Rho-GTPase enzyme involved in T-cell activation
NF-κB pathway		
REL	2p16.1	Proto-oncogene member of the NF-κB family that regulates leukocyte activation and survival
TNFAIP3	6q23.3	Signaling protein and negative regulator of TNF-α–induced NF-κB activation
TRAF1	9q33.1	Regulator of TNF-α–receptor superfamily signaling (e.g., to NF-κB and JNK)
Other pathways		
BLK	8p23.1	B-lymphoid tyrosine kinase involved in B-cell receptor signaling and B-cell development
CCL21	9q13.3	Chemokine implicated in germinal-center formation
FCGR2A	1q23.2	Low-affinity IgG Fc receptor that regulates macrophage and neutrophil activation and immune-complex clearance
PADI4	1p36.2	Enzyme that converts arginine to citrulline, creating autoantigens in rheumatoid arthritis
PRDM1	6q21	Protein that acts as a repressor of β-interferon gene expression
TNFRSF14	1p36.32	TNF-α–receptor superfamily member with proinflammatory activity

* GTPase denotes guanosine triphosphatase, JNK Jun N-terminal kinase, MHC major histocompatibility complex, NF-κB nuclear factor κB, Th17 type 17 helper T cells, and TNF-α tumor necrosis factor α.

† Different *HLA-DRB1* alleles, not only the shared epitope, are associated with rheumatoid arthritis and with distinct immune responses to citrullinated antigens. In addition, *HLA-DP* and *HLA-DQ* loci (outside the *HLA-DRB1* region) have been associated with rheumatoid arthritis.

- HLADRB1 (HLADR4)
  - Alleles that contain a common amino acid motif (QKRAA or shared epitope) in the antigen binding groove of the MHC molecule confer susceptibility to RA



Lancet 2017; 389: 2328–37

Smoking, shared epitope, and risk of RA

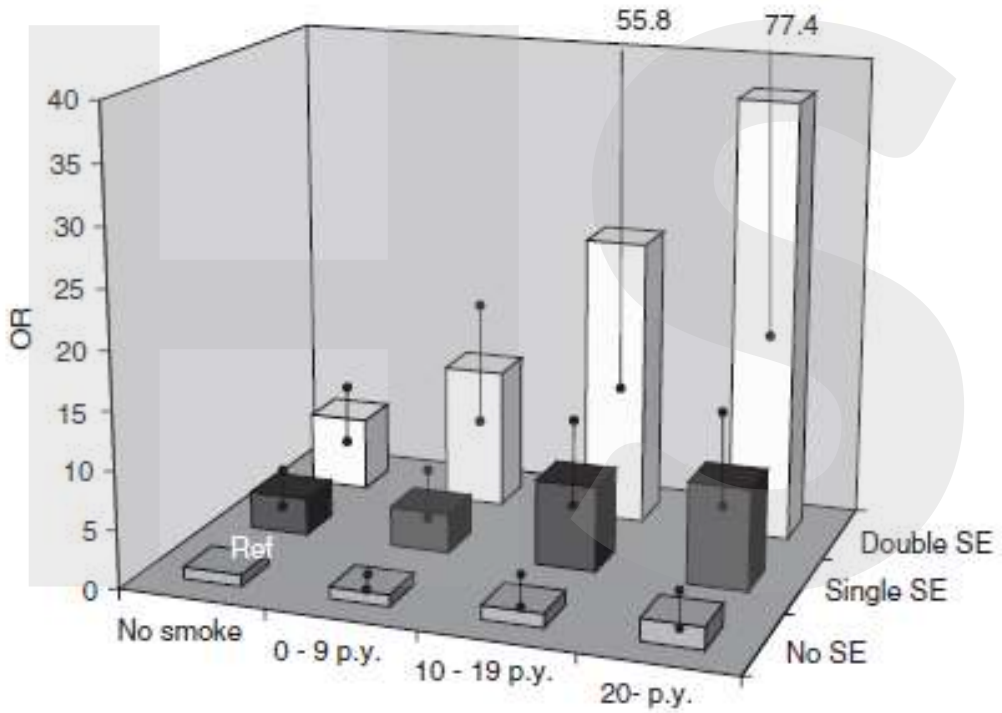
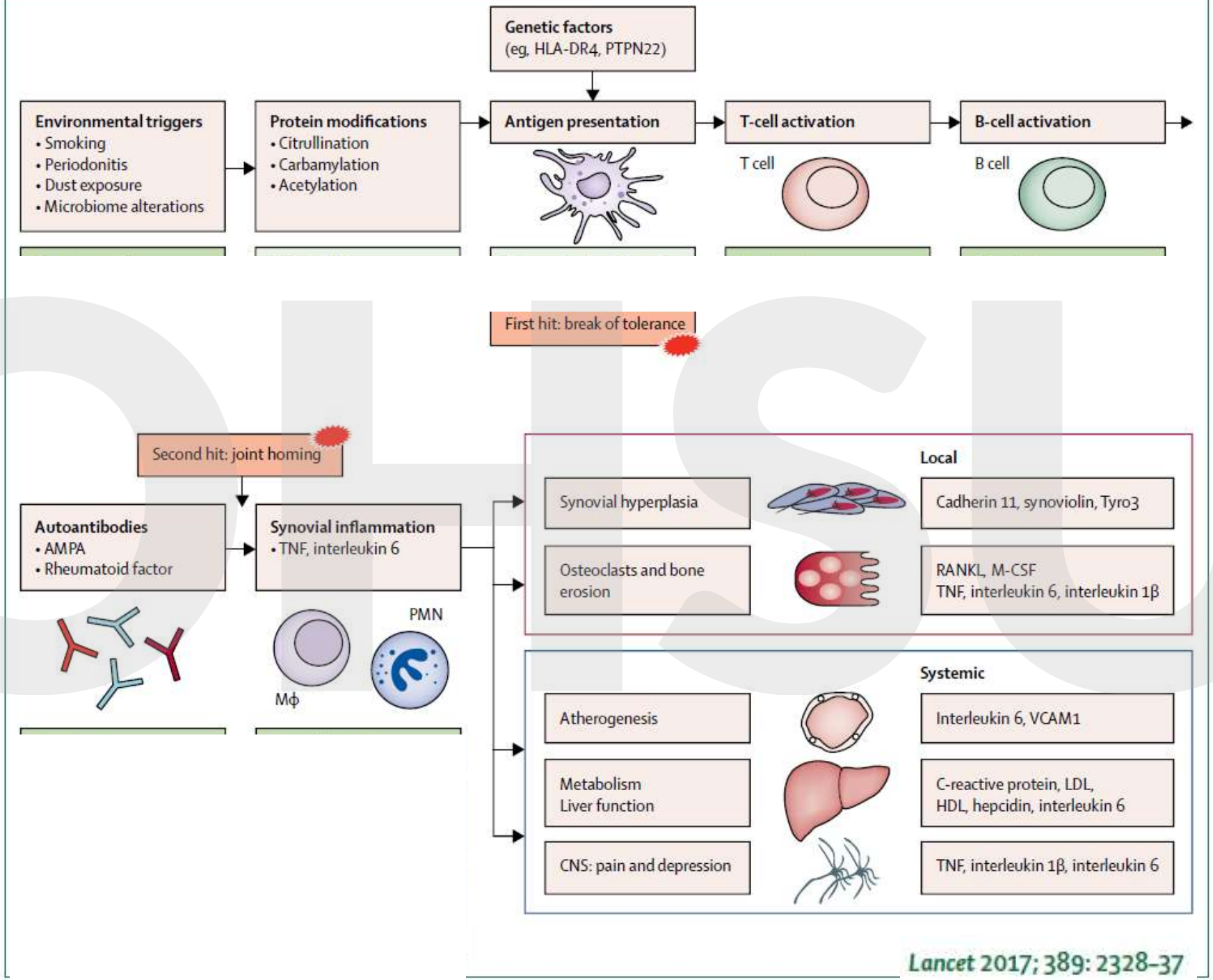


Figure 1 OR for different amounts of smoking (pack years (p.y.)) in combination with none (no shared epitope (SE)), one (single SE) or two (double SE) copies of SE alleles. The reference group was non-smokers without SE alleles.

Kallberg et al. Ann Rheum Dis 2010



Lancet 2017; 389: 2328–37

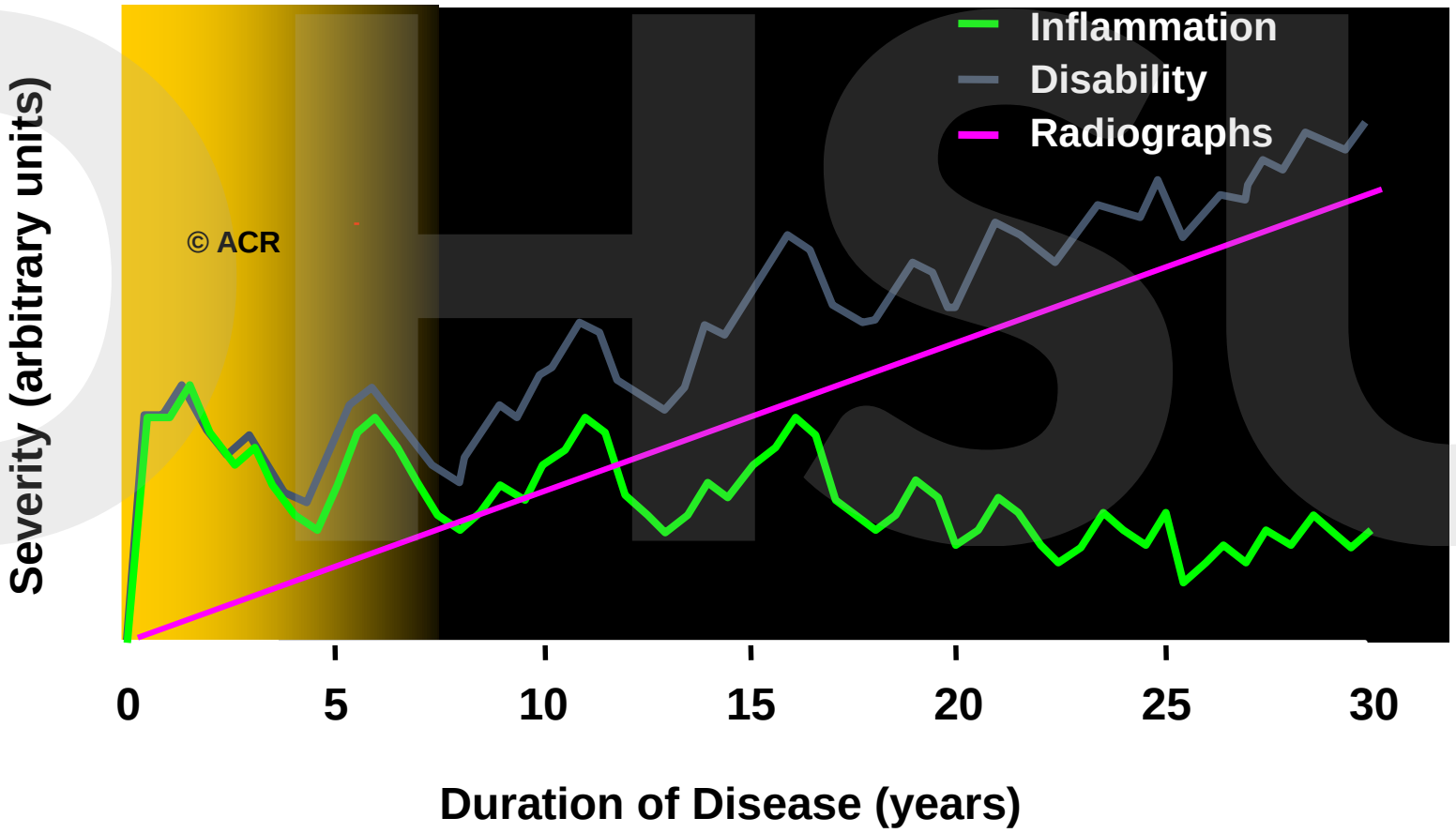
Goals in Treating RA

- Treat symptoms
  - Pain, stiffness, swelling, function
- Prevent long-term disability
  - Structural damage
- Prevent/Manage co-morbidities
  - Infections, cardiovascular risk, osteoporosis

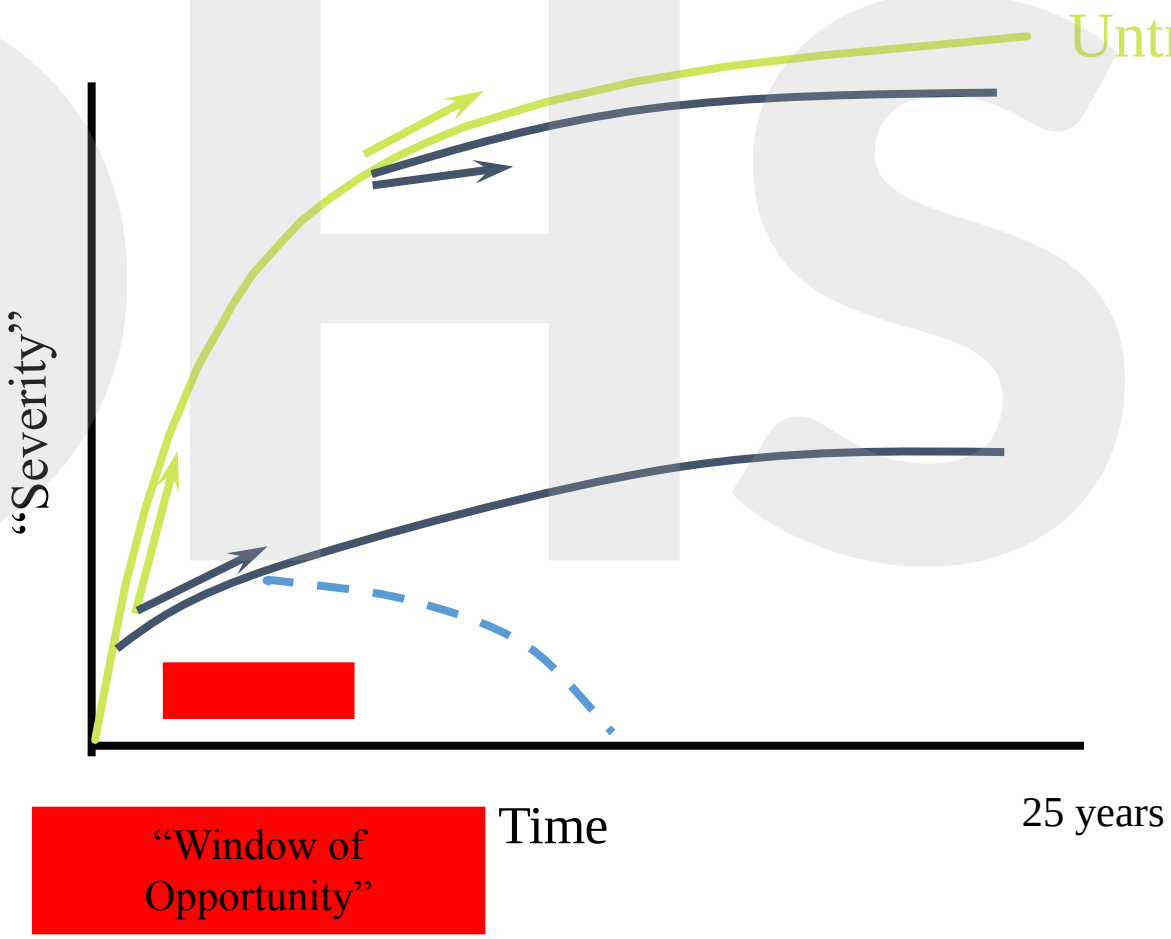
Principles to treatment of RA

- Diagnose early, refer early
- Initiate disease modifying anti-rheumatic drugs (DMARD) early
- Use combination therapy
- Treat-to-target (T2T)
- Aim for remission, or at least for low disease activity

Course of RA Progression

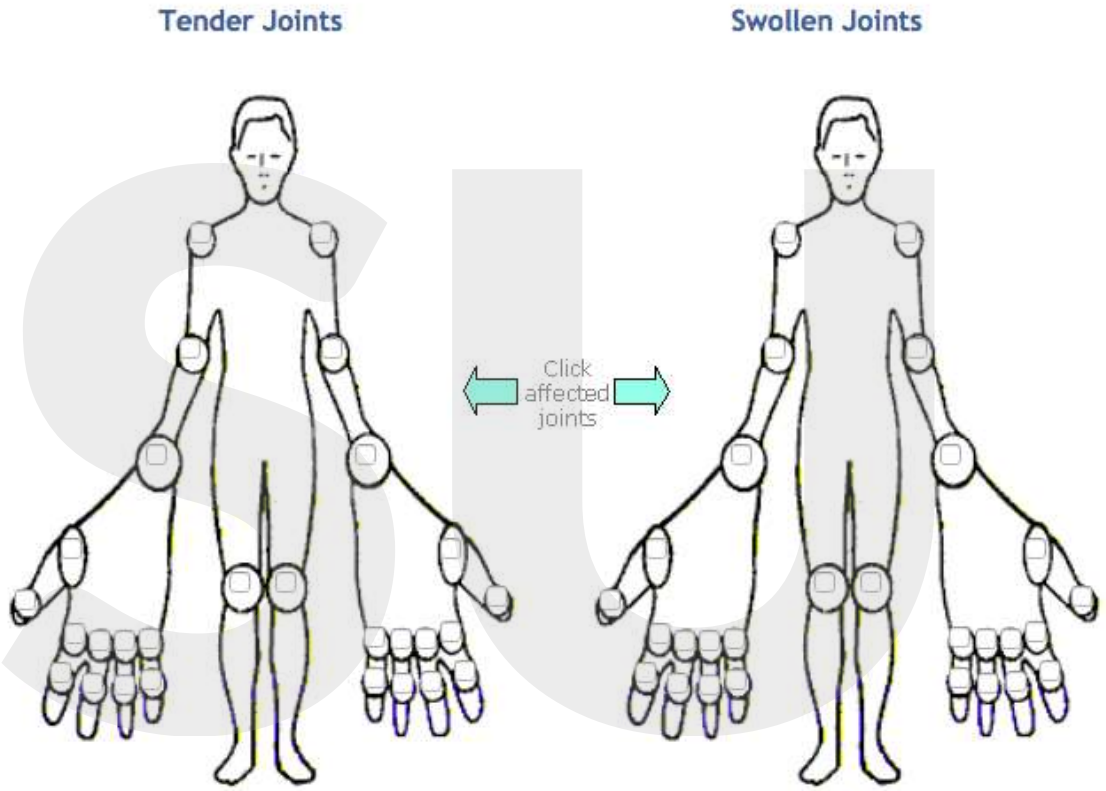


Preventing irreversible joint damage in RA: Window of Opportunity



Evaluation of Response to Treatment in RA

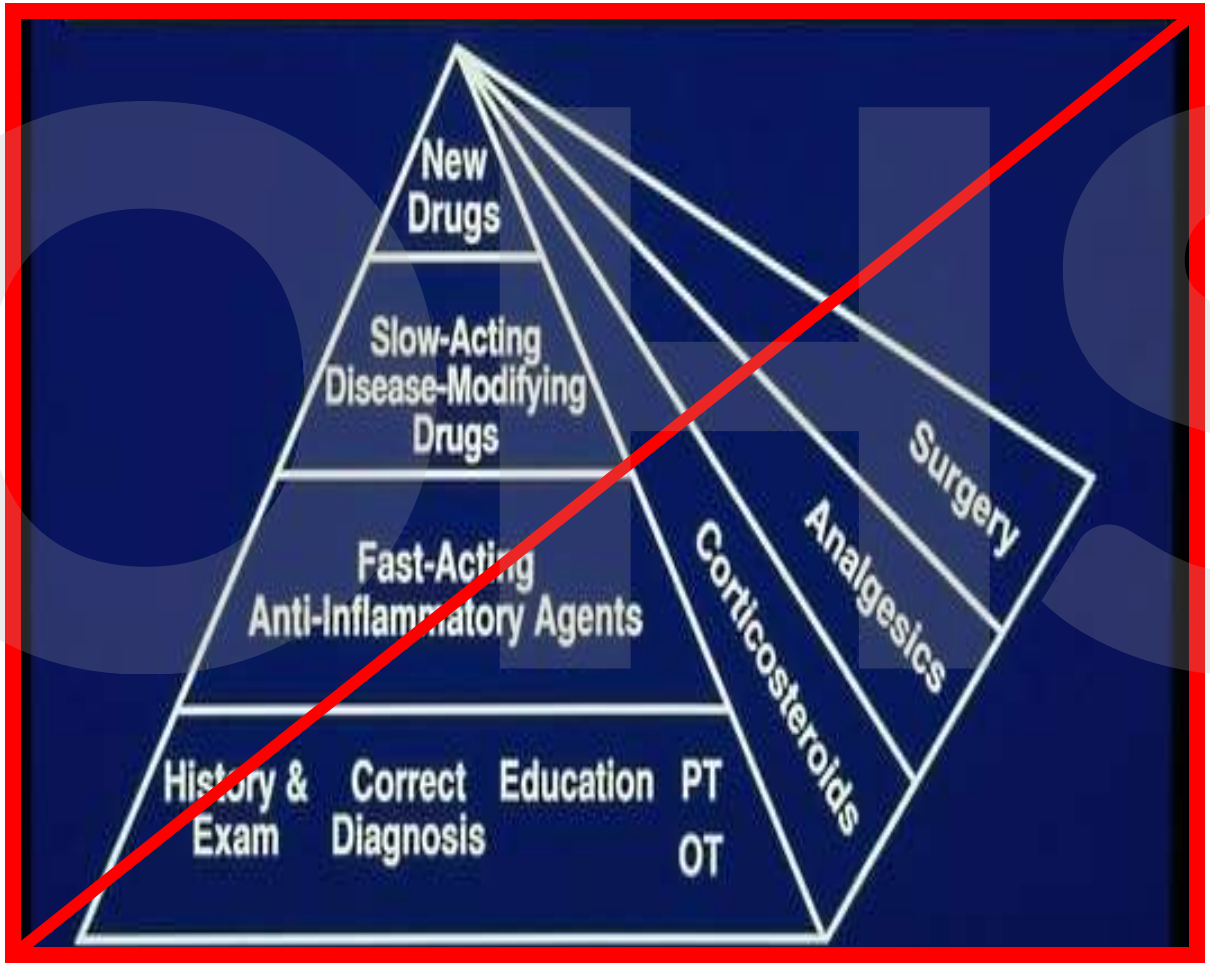
- DAS 28
  - 28 joint count
    - # Swollen joints
    - # Tender joints
    - Global patient assessment (VAS 0-100 mm)
    - ESR



Remission	Low	Moderate	High

0 2.4 3.2 5.2

Turn the Old Treatment Pyramid (1960-90s) upside down



- Start with aspirin or NSAID
- Add a disease modifying anti-rheumatic drug (DMARD) only after damage is detected by X-rays
- Gradually escalate therapy

2012 RA Treatment Algorithm

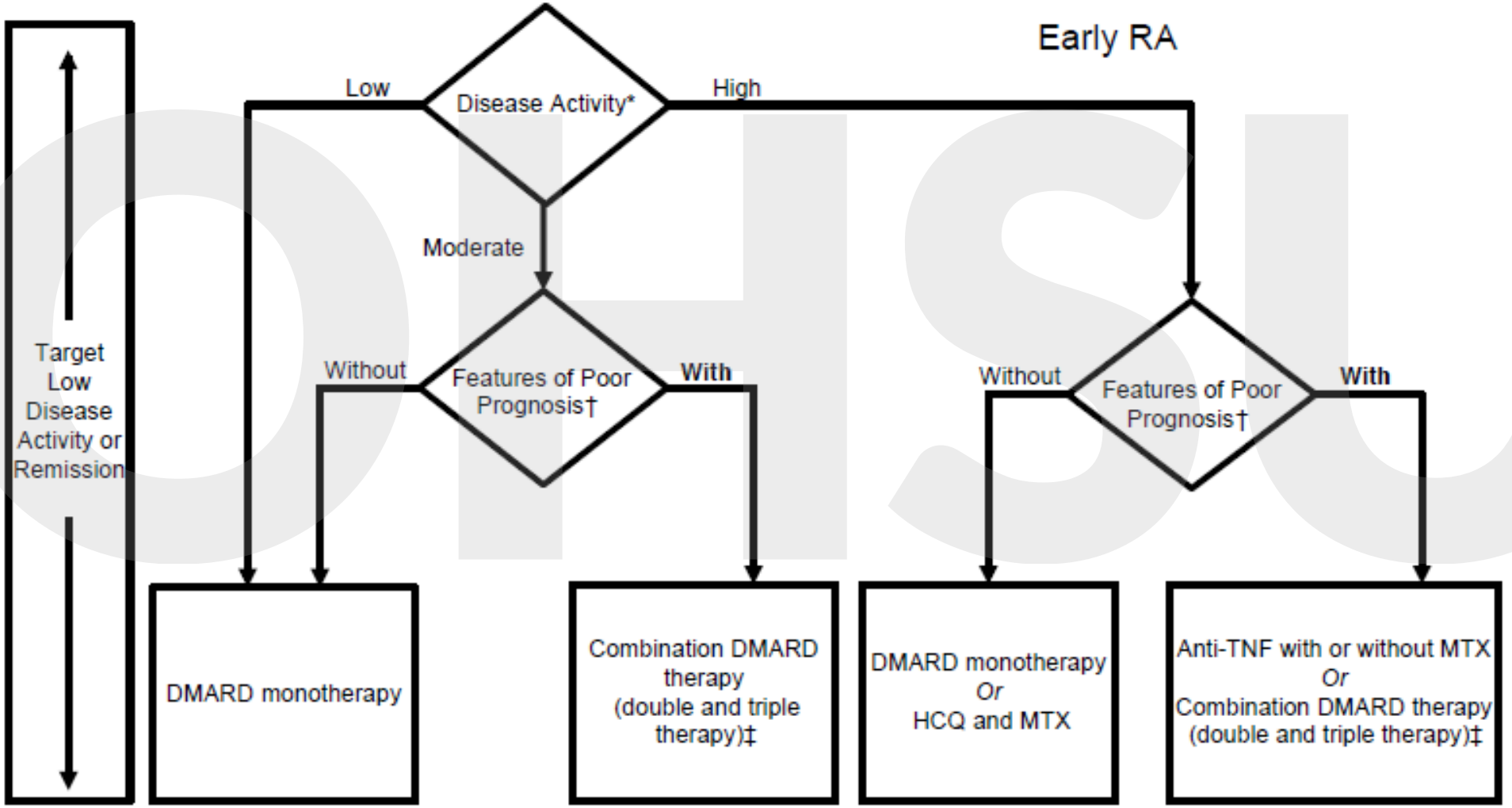


Figure 1. 2012 American College of Rheumatology recommendations update for the treatment of early rheumatoid arthritis (RA),

Singh et al. Arthritis Care & Res 2012; 64(5):625

RA Therapy: Traditional DMARDs

- Methotrexate (most commonly used, core RA drug)
- Hydroxychloroquine
- Sulfasalazine
- Triple therapy (MTX, HCQ, SZA combined)
- Leflunomide

RA Therapy- Biologic DMARDs

- Targeted inhibition of cytokines
  - TNF-alpha: Infliximab, etanercept, adalimumab, golimumab, certolizumab
  - IL-6: Tocilizumab, sarilumab
- Interfering with cytokine activation
  - JAK Kinase: Tofacitinib, Baricitinib
- Block T cell activation
  - CTLA-4Ig: Abatacept
- Deplete B cells
  - Rituximab

What to monitor?

- Lab monitoring
  - Cell counts, liver function, creatinine every 8-12 weeks
- Vigilant for infections
  - Common: Bronchitis, pneumonia, cellulitis
  - Viral: Zoster, influenza, hepatitis B reactivation
  - Atypical: Fungal, mycobacterial (esp. if travel)
- Vigilant for malignancy (skin)
- Vigilant for pulmonary toxicity (any), heart failure (anti-TNF), demyelination (anti-TNF), lupus like reaction (anti-TNF)
- Alcohol excess (methotrexate, leflunomide)
- Eye Exam (Hydroxychloroquine)

Vaccinations

- No live vaccines for patients on immunosuppressive treatment
- Influenza shot yearly
- Pneumonia vaccine (PCV13, PPV23)- best before starting methotrexate or rituximab
- Zoster vaccine- especially for patients on tofacitinib
  - Zostavax is a live vaccine, need to give before starting biologic drug, and wait 3-4 weeks after given to start biologic drug- ok to give while on methotrexate or low dose prednisone (refer to CDC page)
  - Shingrix is not a live vaccine and could be given while receiving biologic therapy in theory though not studied in those patients

Bone Health

- RA and prednisone use are additional risk factor in calculating FRAX score
- Advise on adequate calcium and vitamin D
- Advise on weight bearing or resistive exercise, and fall prevention
- Survey bone density regularly

Perioperative management

- Cervical spine
- Stop NSAIDs
- If on chronic prednisone, consider stress dose hydrocortisone
- Hold biologic medication, or time surgery for the end of the treatment interval; resume 2 weeks post op if no infections or wound complications
- Ok to continue oral DMARD for orthopedic surgeries

What about mortality in RA?

Table 3. Hazard ratios for total mortality for women with RA by serologic phenotype compared to women without RA in the Nurses' Health Study (1976–2012)*

	Deaths	Person-years	Mortality rate†	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)‡
All RA					
No RA	28,501	3,678,801	775	1.00 (reference)	1.00 (reference)
RA	307	17,983	1,707	1.45 (1.30–1.63)	1.40 (1.25–1.57)
Seropositive RA					
No RA	28,492	3,425,924	832	1.00 (reference)	1.00 (reference)
RA	202	10,869	1,858	1.59 (1.38–1.82)	1.51 (1.31–1.74)
Seronegative RA					
No RA	28,501	3,666,676	777	1.00 (reference)	1.00 (reference)
RA	105	7,113	1,476	1.18 (0.97–1.43)	1.15 (0.95–1.39)

* RA = rheumatoid arthritis; HR = hazard ratio; 95% CI = 95% confidence interval.
† Per 100,000 person-years.
‡ Model adjusted for age, questionnaire cycle, census-tract family income (<$40,000 or ≥$40,000 per year), body mass index (<18.5, 18.5–24.9, 25–29.9, or ≥30 kg/m^2), cigarette smoking (never–10, 10.1–20, or >20 pack-years), postmenopausal hormone use (premenopausal, postmenopausal: never postmenopausal hormone use, postmenopausal: past postmenopausal hormone use, or postmenopausal: current postmenopausal hormone use), moderate to vigorous physical activity (0, 0.01–0.99, 1.00–3.49, 3.50–5.99, or ≥6 hours per week), cumulative average of Alternate Healthy Eating Index excluding alcohol component (quintiles), alcohol consumption (0, 0.1–4.9, 5.0–14.9, or ≥15.0 gm/day), cardiovascular disease (yes/no), and aspirin use (yes/no). Covariates were updated up to death, end of study period, censor, or loss to follow-up, whichever came first.

Sparks et al AC&R 2015

- Increased mortality associated with duration of rheumatoid arthritis
- Serologic status with greater risk of mortality in seropositive patients

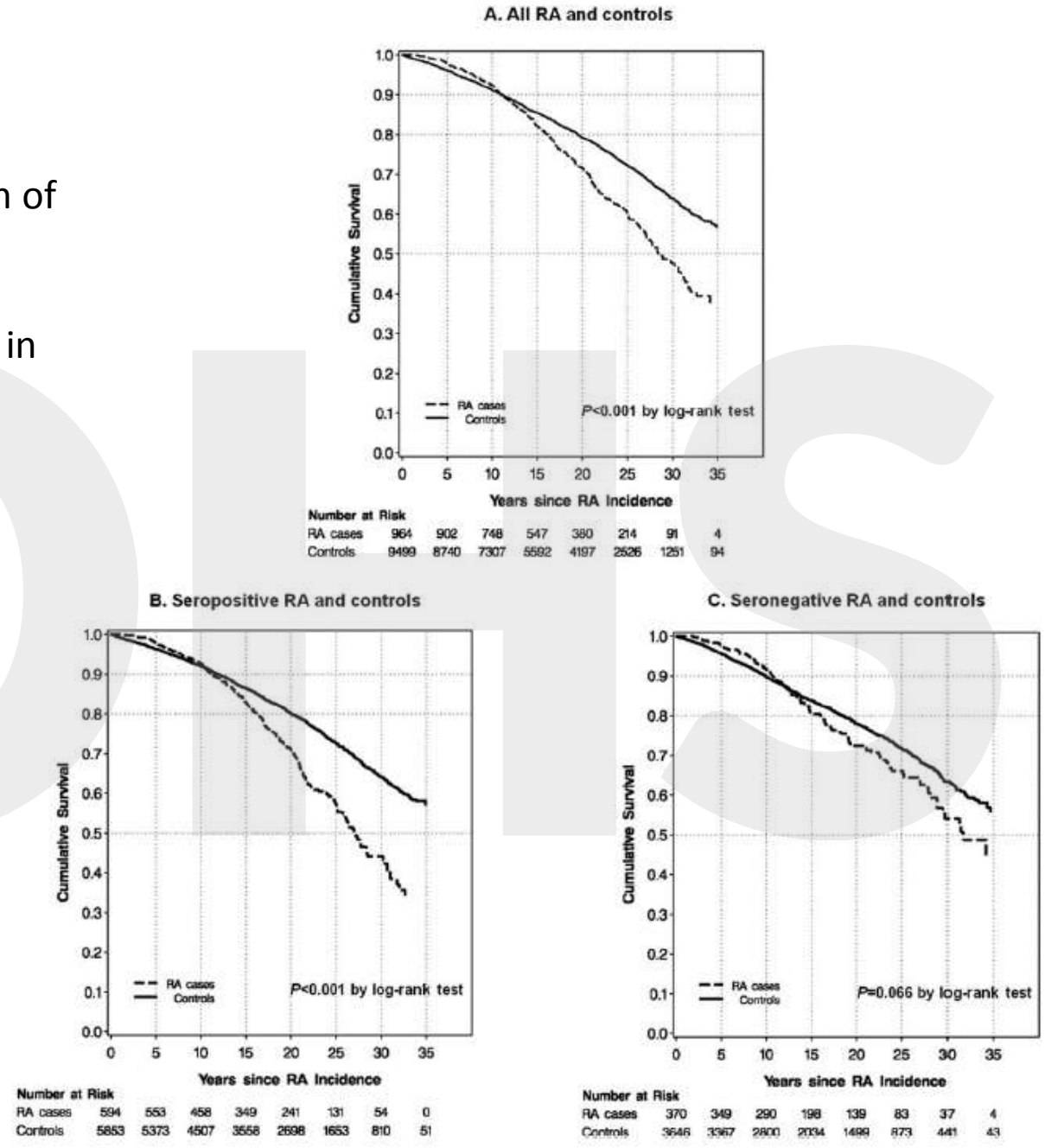


Figure 2. Kaplan-Meier curves for survival after incident rheumatoid arthritis (RA) diagnosis and age- and period-matched controls at index date of RA diagnosis for women in the Nurses' Health

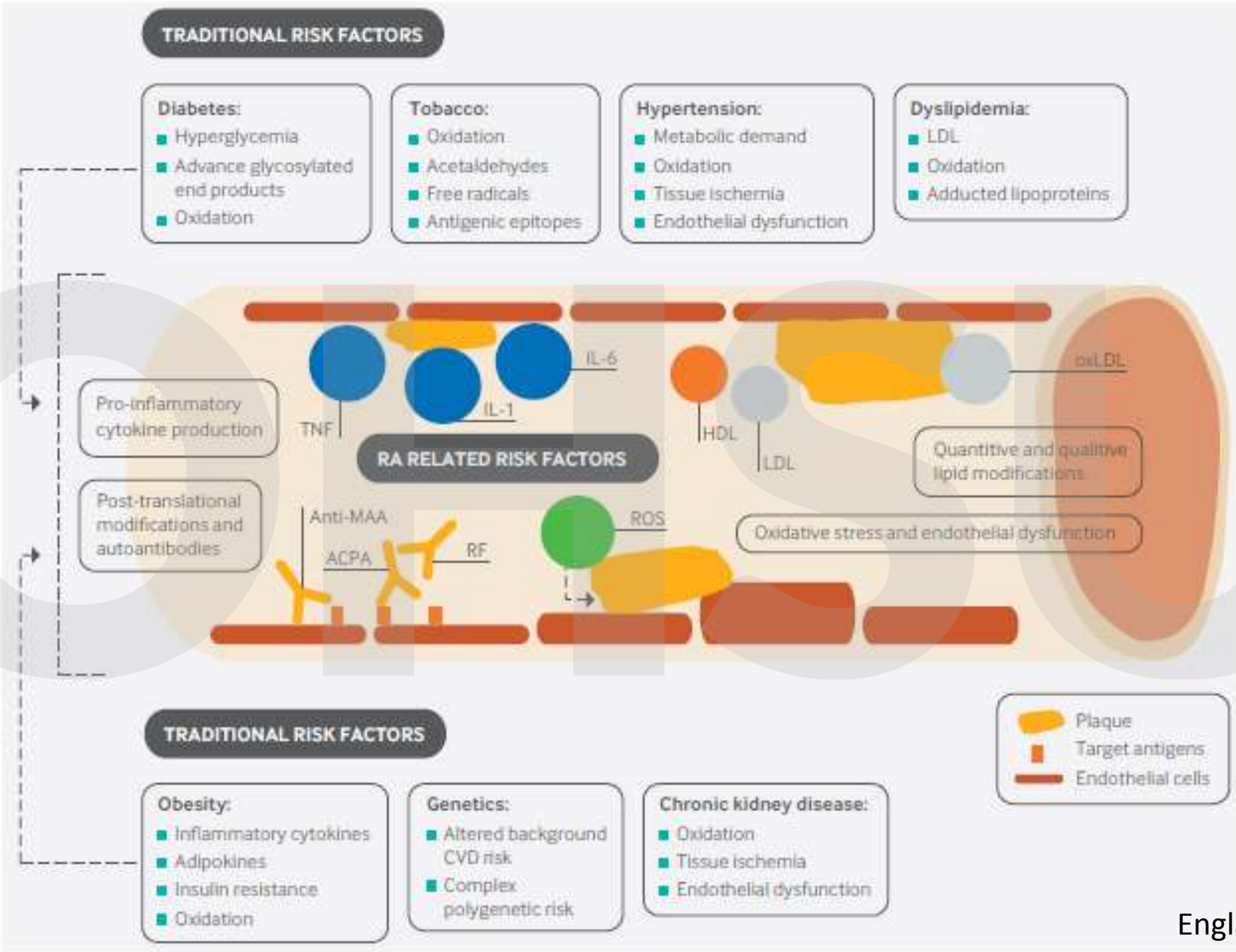
Sparks et al AC&R 2015

Table 4. Hazard ratios for cause-specific mortality for women with incident RA by serologic phenotype compared to women without RA in the Nurses' Health Study (1976–2012)*

	Cancer mortality		Cardiovascular mortality		Respiratory mortality	
	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)†	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)†	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)†
All RA						
No RA	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
RA	1.00 (0.80–1.25)	0.93 (0.74–1.15)	1.49 (1.18–1.89)	1.45 (1.14–1.83)	2.57 (1.91–3.48)	2.06 (1.51–2.80)
Seropositive RA						
No RA	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
RA	0.95 (0.71–1.26)	0.86 (0.65–1.15)	1.39 (1.02–1.90)	1.41 (1.03–1.93)	3.55 (2.55–4.95)	2.67 (1.89–3.77)
Seronegative RA						
No RA	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
RA	1.01 (0.72–1.42)	0.96 (0.68–1.35)	1.55 (1.08–2.21)	1.41 (0.98–2.02)	1.09 (0.54–2.19)	0.98 (0.49–1.99)

* RA = rheumatoid arthritis; HR = hazard ratio; 95% CI = 95% confidence interval.
† Model adjusted for age, questionnaire cycle, census-tract family income (<$40,000 or ≥$40,000 per year), body mass index (<18.5, 18.5–24.9, 25–29.9, or ≥30 kg/m^2), cigarette smoking (never–10, 10.1–20, or >20 pack-years), postmenopausal hormone use (premenopausal, postmenopausal: never postmenopausal hormone use, postmenopausal: past postmenopausal hormone use, or postmenopausal: current postmenopausal hormone use), moderate to vigorous physical activity (0, 0.01–0.99, 1.00–3.49, 3.50–5.99, or ≥6 hours per week), cumulative average of Alternate Healthy Eating Index excluding alcohol component (quintiles), alcohol consumption (0, 0.1–4.9, 5.0–14.9, or ≥15.0 gm/day), cardiovascular disease (yes/no), and aspirin use (yes/no). Covariates were updated up to death, end of study period, censor, or loss to follow-up, whichever came first.

Sparks et al AC&R 2015



England et al BMJ 2018

Fig 1| Overview of mechanisms of cardiovascular disease (CVD) in rheumatoid arthritis (RA). Several mechanisms interact to amplify risk of CVD in RA. Higher RA

Doing better…

Data from Olmsted County, MN

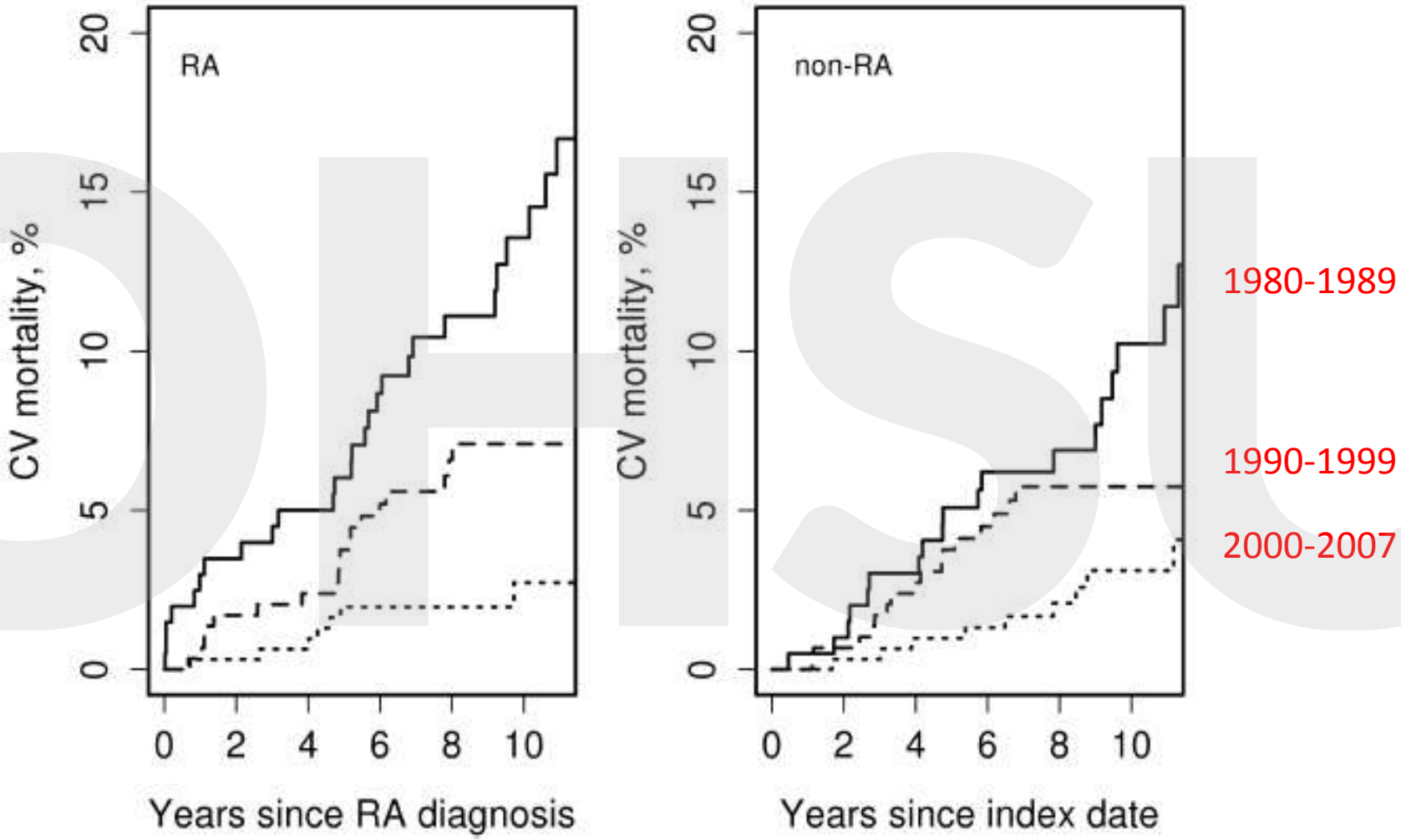


Figure 2. CV mortality in subjects with and without RA by decade of RA incidence/index: 1980–89 (solid line), 1990–99 (dashed line), and 2000–07 (dotted line). CV: cardiovascular; RA: rheumatoid arthritis.

Myasoedova et al. J Rheum 2017

England et al BMJ 2018

Take Home Messages

- Diagnose and refer RA early
- Think of atypical presentations
- Labs and x-rays not always supportive, so rely on history and exam
- Key to treating RA is early initiation of disease modifying drugs
- Treating with prednisone and NSAIDs only is not acceptable
- DMARDs prevent joint damage, extra-articular complications, and cardiovascular disease and likely improve mortality
- Have a low threshold to evaluate for infection
- Assess safety labs, bone health, vaccinations

Questions?

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